Remarks

Applicants filed a response to the office action dated November 12, 200. The USPTO issued a Notice of non-compliant amendment on August 12, 2005. Applicants provide this Response to collectively address issues in the November 12, 2004 office action and August 12, 2005 Notice.

Claims 1, 3-96, 100-191, 193-196, 200-214 and 216-223 are pending in the subject application. Applicant expresses his gratitude to the Examiner for the courtesy extended during the April 7, 2005 interview ("April Interview"). Applicant files separately a supplemental Information Disclosure Statement providing copies of references cited in the tables provided with the Declaration of Henry Daniell, PhD ("Daniell Declaration"). The Daniell Declaration is also filed separately and will follow this response. The tables were discussed with the Examiner during the April interview.

At pages 2-3, the office action points out typographical and grammatical errors of claims 214, 217-218 and 220-223. The Applicant has addressed these errors by the amendments to these claims provided above. Claim 214 has been amended to change "form" to –from--. Claims 194 and 214 have been amended to address typographical and grammatical issues raised in the August 12, 2005 Notice. Claims 217, 218 and 220-221 have been amended to address the noun/verb agreement to read --control sequences ... further comprise--. Claim 222 has been amended to correct "sequence" to read – sequences--. None of these amendments effect the scope of the claims. Claim 223 has been amended to remove non-elected subject matter as the Examiner pointed out, i.e., specific reference to herbicide resistance genes.

Applicant acknowledges that the Examiner finds support for unconserved transcriptionally active intergenic spacer regions. Furthermore, claims 190 and 191 have been amended to recite that the chloroplast DNA flanking sequences are derived from a transcriptionally active spacer region. The distinctions between transcriptionally active,

transcriptionally silent and read-through spacer regions are explained in the Daniell Declaration. The indefinite article --a-- has been added to claims before the phrase "higher species", and is intended to have its commonly understood meaning. See *Scanner Tech.*, 365 F.3d 1299, (Fed. Cir. 2004). Also, in claim 191 the indefinite article --a-- has been inserted before the word "control" so as to improve the grammatical syntax. This inserted "a" also is to be interpreted to have its commonly understood meaning.

Claims 118-119, 122, 214 and 223 are rejected under 35 USC 112, second paragraph, as being indefinite. Claim 118 has been amended to remove the redundant phrase "wherein the peptide of interest is a biologically active molecule." The dependency of claim 122 has been corrected to now depend from claim 118. Claim 214 has been amended to correct the antecedent basis problem by removing "said" immediately preceding "homologous". Claim 223 has been amended as stated above. The basis of this rejection being obviated, Applicant respectfully requests reconsideration of the 35 USC 112, second paragraph rejection.

Claims 214 and 222-223 are rejected under 35 USC 112, first paragraph as containing new subject matter. Applicants believe that the amendment to claim 214 above obviates this rejection. Claim 214 has been amended to remove the recitation "wherein the control sequence positioned upstream form the 5' end of the first heterologous DNA sequence is an origin of replication". Applicant requests reconsideration of this rejection.

Claims 3, 171, 190-191, 193, 196 214 and 216-223 are rejected under 35 USC 112, first paragraph as lacking enablement. Applicants respectfully traverse. As the Examiner correctly pointed out in the interview summary mailed on April 13, 2005, the Applicant's fundamental basis for why the rejected claims are enabled is as follows:

(1) Given the art's knowledge of the limited number of transcriptionally active spacer regions, in light of the art's familiarity with the Sugita et al. reference (of record),

the skilled artisan could straightforwardly test transcriptionally active regions, in addition to the intergenic spacer 2 region, and determine their utility as viable spacers for chloroplast transformation without undue experimentation.

(2) Integration of heterologous DNA into a transcriptionally active spacer region exemplified in the present application has been dramatically successful as demonstrated by the results provided in the present application and numerous documented efforts after the filing date of the present application. References showing such results are provided in Table I attached hereto.

(3) Success by others showing successful integration of heterologous DNA into transcriptionally silent and read-through spacer regions. These successes demonstrate that, in light of the teachings of the present application, and the fact that other transcriptionally related spacer sequences were known at the time of filing, integration of DNA into other transcriptionally active spacer regions does not require undue experimentation.

Claims 190 and 191 have been amended to recite that the DNA flanking sequences are derived from a transcriptionally active spacer region. The Examiner has expressed that it would be helpful to explain the differences between read-through and transcriptionally active regions, including differences in transcription efficiency such regions. Applicant submits the Daniell Declaration for this purpose, and to provide further expert testimony discussing the fundamental position that post-filing successes of integration of heterologous DNA into many other spacer regions demonstrates that development of transcriptionally active spacer regions, in addition to that specifically utilized in the examples of the present application, is achievable without undue experimentation.

There are a number of known transcriptionally active spacer regions that are present in the chloroplast genome. See Daniell Declaration and previous discussion on the Sugita et al. (1996) reference (of record), which discusses 60 "transcriptionally active" sites. Figure 2B teaches the construction of a vector that is adapted for integration into the intergenic spacer 2 region. One employing basic molecular biology

techniques could implement similar construct for a different transcriptionally active region by simply substituting the flanking DNA sequences shown in Fig 2B with flanking sequences derived from a different spacer region. The vector could be introduced into the chloroplast and successful transformation confirmed via the techniques taught in the specification. Though testing one or more of these sites might require some experimentation, such experimentation would be relatively straightforward. The fact that some experimentation is required does not elevate such an endeavor to the legal threshold of "undue experimentation." Furthermore, any concern about the ability to develop a particular spacer region is alleviated by the many studies that have been conducted by others since the filing of the subject application.

Table II (Exhibit C of Daniell Declaration) lists numerous studies implementing transcriptionally silent and read-through regions, as well as some transcriptionally active spacer regions, for the integration of heterologous DNA. Applicant acknowledges that the majority of these studies focused on implementation of transcriptionally silent and read-through regions. On this point, certainly it is fair to state that the development of a particular transcriptionally silent or read-through spacer region can be achieved through routine experimentation. Though, in some respects, the structural framework of transcriptionally silent and read-through regions is distinct from transcriptionally active regions, the fundamental molecular principles of transcription and genetics apply equally to all three types. Thus, one may conclude that the implementation of different transcriptionally active regions would require no more experimentation or skill as that which has already been shown for the testing of transcriptionally silent and read-through regions. From a scientific perspective, there is nothing uniquely difficult about testing transcriptionally active regions compared to transcriptionally silent or read-through regions. See Daniell Declaration, paragraph 4. Indeed, the fact that many others have tried and have been successful at testing and implementing transcriptionally silent and read-through regions directly supports Applicant's assertion that transcriptionally active spacer regions other than the intergenic spacer 2 region may also be tested and successfully implemented. Daniell Declaration, paragraph 4.

Though Applicants are unaware of studies directed to use of transcriptionally active sites other than the intergenic 2 spacer region, this is not a result of the ease or difficulty of utilizing transcriptionally active spacer regions other than the intergenic 2 spacer region. Rather, it is reasonable to conclude that this is a result of two primary factors. First, the intergenic spacer 2 region has been so well characterized and works so well that there is little motivation to test other transcriptionally active spacer regions. Table I illustrates the numerous successes of implementing the intergenic spacer 2 region. Second, given the stature of the inventor in the field, and the presence of issued patents held by inventor, other laboratories are deterred from entering territory already so well captured by the Applicant. The Applicant is one of the eminent experts in the field of chloroplast transformation. He has numerous articles published in widely known and respected scientific journals. Furthermore, the Applicant already has been granted key patents in the chloroplast transformation area. See, e.g., U.S. Patent Nos. 5,693,507; and 5,932,479. Frankly, the absence of work by other laboratories to characterize other transcriptionally active sites is not surprising. Other investigators are undoubtedly aware of the inventor's expansive progress in this area from both a research and patenting perspective. Relying on the availability of studies on other transcriptionally active spacer would ultimately serve to penalize Applicant for his extensive work and successes in this field.

Claims 3 and 171 are dependent on claim 190, and any enablement issues of claims 3 and 171 are addressed by the remarks made above regarding enablement of claim 190. As to the enablement of claims 214, 217-218 and 220-221, these claims have been amended to more clearly recite that the control sequences comprise a chloroplast origin of replication sequence. Applicants believe that the amendments to these claims obviate any enablement issues. Further, the remarks made above and in the Daniell Declaration pertaining to the meaning of transcriptionally active obviate the Examiner's concern about the origin of flanking DNA sequences. Accordingly, in view of the foregoing remarks and amendments, Applicant respectfully requests reconsideration and withdrawal of the 35 USC § 112, first paragraph rejection.

Claims 3, 171, 190, 191, 193, 196, 214 and 216-223 are rejected under 35 USC § 112, first paragraph on the alleged grounds of lacking written description. Applicants traverse. As was discussed during the April Interview, the issue of conservation of the DNA flanking sequence no longer applies to the rejected claims. The rejected claims do not recite that the DNA flanking sequences are conserved. As to the support for unconserved transcriptionally active spacer regions, Applicants reiterate that the subject application provides support for such regions, as has already been acknowledged by the Examiner. See page 2 of the latest Office Action. Accordingly, reconsideration of this 35 USC § 112, first paragraph, rejection is respectfully requested.

Claims 3, 171, 190-191, 196, 214 and 216-223 are rejected under 35 USC § 102(b) as being anticipated by Staub et al. Applicants respectfully traverse. Claims 190 and 191 recite that the DNA flanking sequences are derived from a transcriptionally active region. Thus, these DNA flanking sequences direct integration of heterologous DNA into a transcriptionally active spacer region of the chloroplast genome. The Staub et al. reference does not teach or suggest use of DNA flanking sequences derived from a transcriptionally active spacer region nor integration of heterologous DNA into a transcriptionally active spacer region. Accordingly, the Staub et al. reference does not satisfy the requirements for anticipation. Dependent claims 3, 171, 216-218 are construed to contain the limitations of claim 190 and are therefore also not anticipated by the Staub et al. reference.

Claim 196 has been amended to clarify that "stable integration of the heterologous DNA sequence into the chloroplast genome ... is directed into a transcriptionally active intergenic spacer region of the chloroplast genome." Staub et al. discloses integration into a read-through region. Accordingly, Staub et al. is distinct from the invention recited in claim 196, and does not anticipate claim 196. Claims 219-221 depend from claim 196 and therefore are construed to contain the limitations of claim 196. As the Staub et al. reference does not anticipate claim 196, it also does not anticipate dependent claims 219-221.

Claim 214 recites that stable integration [of the heterologous DNA] is directed into a transcriptionally active intergenic spacer region of the chloroplast genome. Again, it is noted that the Staub et al. reference does not teach integration into transcriptionally active regions. Thus, it does not teach all of the elements of claim 214 as required for anticipation. Claims 222, and 223 are construed to contain the limitations of claim 214 from which they depend. Thus, such dependent claims are not anticipated by the Staub et al reference. Reconsideration and withdrawal of this 35 USC § 102(b) are requested.

Claims 3, 171, 190-191, 196, 214 and 216-223 are rejected under judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-23, 25-29, 31 and 34 of U.S. Patent No. 5,923,479 ('479 patent). With respect to claim 191, none of the claims cited from the '479 patent render obvious the inclusion of a heterologous gene of interest and selectable marker where the expression of either is driven by a control sequence upstream from the 5' end of the gene of interest and transcription is terminated by a control sequence downstream from the 3' end of the selectable marker. Further, claim 3, which depends from claim 191, is construed to contain the limitations of claim 191.

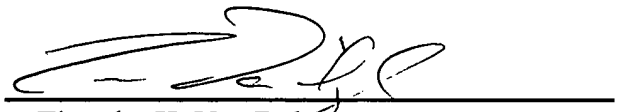
Claim 214 recites that transcription is driven by a chloroplast promoter at the transcriptionally active intergenic spacer region. The claims of the '479 patent do not render obvious a construct that utilizes an endogenous chloroplast promoter. This also applies to claims 215, 222 and 223 which directly or indirectly depend from claim 214. Claim 216 recites that the expression cassette further comprises at least one additional heterologous DNA sequence operably joined to the 3' end of said heterologous DNA sequence and upstream of the 3' controlling sequence. The claims of the '479 patent do not render obvious an arrangement where there are two heterologous sequences controlled by the same downstream controlling sequence. This applies also to claim 218 which depends from claim 216.

Though the cited claims from the '479 patent may generically encompass integration into transcriptionally active spacer regions, the specific recitation of

integration into a transcriptionally active region such as for claims 190, 196 and dependent claims 171, 216, 217 and 218 and 219-221, respectfully, is not an insignificant advancement in the field. As discussed above, the integration into a transcriptionally active region flew in the face of the well-established dogma in the field at the time of filing that transformation into transcriptionally active regions must be avoided. It is unfair for the office action to glibly assert that integration of the expression cassette into a specific genomic region is merely an intended use and is not given patentable weight. The integration into a transcriptionally active region is directly tied to and is a function of the flanking sequences which are a structural part of the vector. Reconsideration of the obviousness-type double patenting rejection is respectfully requested.

All grounds for rejection or objection having been addressed and overcome herein, it is respectfully urged that this application is in condition for allowance. Applicants request that the Examiner call the undersigned if clarification is needed on any aspect of this Reply, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application.

Respectfully submitted,



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CERTIFICATE OF MAILING

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